

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Gary A. Beaudry and Paul J. Maddon

Serial No. : 07/960,440

Filing Date : December 8, 1992

For : CD4-GAMMA2 AND CD4-IgG2 CHIMERAS

30 Rockefeller Plaza
New York, New York 10112

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Attn: Licensing and Review

SIR:

DECLARATION IN RESPONSE TO JULY 13, 1993 NOTICE
CONCERNING THE ATOMIC ENERGY ACT OF 1954 (42 U.S.C. §2182)

We, the undersigned, Gary A. Beaudry, a citizen of the United States of America, residing at 109 Inwood Avenue, Upper Montclair, New Jersey 07043, U.S.A., and Paul J. Maddon, a citizen of the United States of America, residing at 60 Haven Avenue, New York, New York 10032, U.S.A, declare as follows:

OK H

1. We jointly made and conceived the invention described and claimed in patent application Serial Number 07/960,440, filed in the United States of America on December 8, 1992, entitled "CD4-GAMMA2 AND CD4-IgG2 CHIMERAS."
2. We made and conceived this invention while employed full-time by Progenics Pharmaceuticals, Inc. This invention is related to the work we are employed to perform and was made within the scope of our employment duties. This invention was made with the use of facilities, equipment, materials, funds, information and services of Progenics Pharmaceuticals, Inc.

Applicants: Gary A. Beaudry and Paul J. Maddon
U.S. Serial No.: 07/960,440
Filed: December 8, 1992
Page 2

3. This invention was not made or conceived in the course of, or in connection with, or under the terms of any contract, subcontract or arrangement entered into with or for the benefit of the United States Atomic Energy Commission or its successors, the Energy Research and Development Administration or the Department of Energy.

We further declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

August 4, 1993
Date



Gary A. Beaudry

Date

Paul J. Maddon

Applicants: Gary A. Beaudry and Paul J. Maddon
U.S. Serial No.: 07/960,440
Filed: December 8, 1992
Page 2

3. This invention was not made or conceived in the course of, or in connection with, or under the terms of any contract, subcontract or arrangement entered into with or for the benefit of the United States Atomic Energy Commission or its successors, the Energy Research and Development Administration or the Department of Energy.

We further declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

Date

Gary A. Beaudry

August 4, 1993
Date

Paul J. Madden
Paul J. Madden

AS
01/960440

#2

JOHN P. WHITE
 COOPER & DUNHAM
 30 ROCKEFELLER PLAZA
 NEW YORK, NEW YORK 10112

UNITED STATES DESIGNATED/ELECTED
 OFFICE (DO/EO/US)
**NOTIFICATION OF ACCEPTANCE OF
 APPLICATION UNDER 35 U.S.C 371
 AND 37 CFR 1.494 OR 1.495**

Date of Mailing

29 JUN 93

File Reference

37690-II-PCT-US

IDENTIFICATION OF THE INTERNATIONAL APPLICATION

International application Number	International filing date	Priority date claimed
PCT/US92/01143	10 FEB 92	08 FEB 91

Applicant for DO/EO/US

BEAUDRY, GARY A. ET AL.

NOTIFICATION

The applicant is hereby advised that the United States Patent and Trademark Office in its capacity as a Designated Office, Elected Office, has determined that the above identified international application has met the requirements of 35 U.S.C. 371 and 37 CFR 1.494, 1.495 and is ACCEPTED for national patentability examination in the United States Patent and Trademark Office.

The United States Serial Number assigned to the application and the relevant dates are:

11/960440

8 Dec. '92

8 Dec. '92

U.S. NATIONAL SERIAL NO.	35 U.S.C. 102(c) DATE	DATE OF RECEIPT 35 U.S.C. 371 REQUIREMENTS
--------------------------	-----------------------	---

A request for immediate examination under 35 U.S.C. 371 (f) was received on 8 Dec. '92 and the application will be examined in turn.

No request for immediate examination under 35 U.S.C. 371 (f) was received. The application will not be processed or examined before the time limit set forth in either PCT Article 23 (Chapter I of the PCT), or PCT Article 40 (Chapter II of the PCT) whichever is applicable.

UNITED STATES DESIGNATED/ ELECTED OFFICE

ADDRESS ONLY:
 COMMISSIONER OF PATENTS AND TRADEMARKS
 Box PCT, Attn: DO/EO/US
 Washington, D.C. 20231

AUTHORIZED OFFICER

Allan Salyards

FEES SUBMITTED OR AUTHORIZED
Non-Small Entity Patent Processing Fees
 NOTE: Please stamp file
 FILED UNDER 35
 USC 371

11/960440

SEB	CODE	CASH	CHARGE
Basic		\$ 00	\$ 00
		\$ 00	\$ 00
	960	\$ 00	\$ 00
		\$ 00	\$ 00
		\$ 00	\$ 00
Each Independent Claim in EXCESS OF 3	964	\$ 00	\$ 00
Claim(s) in EXCESS OF 20	966	\$ 00	\$ 00
Multiple Dependent Claims	968	\$ 00	\$ 00
Surcharge for Late Fees/Oath or Declaration	134	\$ 00	\$ 00

Small Entity Patent Processing Fees

SEB	CODE	CASH	CHARGE
Basic		\$ 00	\$ 00
		\$ 00	\$ 00
	961	\$ 355 355 00	\$ 00
		\$ 00	\$ 00
Each Independent Claim in EXCESS OF 1	963	\$ 37 00	\$ 00
Claim(s) in EXCESS OF 20	967	\$ 00 00	\$ 00
Multiple Dependent Claims	969	\$ 115 00	\$ 00
Surcharge for Late Fee/Oath or Declaration	234	\$ 65 00	\$ 00

Other Fees - NO SMALL ENTITY REDUCTION

SEB	CODE	CASH	CHARGE
Surcharge for Late Trans.	136	\$ 00	\$ 00
Assignment	581	\$ 40 00	\$ 00

Total Cash - \$ 682 :
 (612)

Total Charge - \$ 682 :
 (612)

AS



73 Rec PCT/TO 8 DEC 1992

11/960440

PCT

Dkt. 37690-II-PCT-US/JPW/AJM

IN THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US)

Applicants: Gary A. Beaudry and Paul J. Maddon

Serial No.: Not Yet Known Int'l Appln. No.: PCT/US92/01143

Filed : Herewith Int'l Filing
Date: February 10, 1992

For : CD4-GAMMA2 AND CD4-IgG2 CHIMERAS

30 Rockefeller Plaza
New York, New York 10112
December 8, 1992

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

ATTN: DO/EO/US

Sir:

**EXPRESS MAIL
CERTIFICATE OF MAILING
FOR ABOVE-IDENTIFIED APPLICATION**

Express Mail mailing label number GB079782318US
Date of Deposit December 8, 1992

I hereby certify that these papers in connection with the
above-identified application are being deposited with the
United States Postal Service "Express Mail Post Office to
Addressee" service under 37 C.F.R §1.10 on the date
indicated above and is addressed to the Commissioner of
Patents and Trademarks, Washington, D.C. 20231 to the
attention of DO/EO/US.

Printed Name

John P. White
John P. White, Esq.
Reg. No. 28,678
Attorney for Applicants
Cooper & Dunham
30 Rockefeller Plaza
New York, N.Y. 10112
(212) 977-9550

HOME COPY
INTERNATIONAL APPLICATION
UNDER THE
PATENT COOPERATION TREATY

REQUEST

THE UNDERSIGNED REQUESTS THAT THE PRESENT
 INTERNATIONAL APPLICATION BE PROCESSED
 ACCORDING TO THE PATENT COOPERATION TREATY

(The following is to be filled in by the receiving Office)

**INTERNATIONAL
 APPLICATION NO.**

PCT/US/201143

**INTERNATIONAL
 FILING DATE:**

10 FEB 1992

PCT INTERNATIONAL

APPLICATION RO/US

(Stamp)
 Name of receiving Office and date of filing

Applicant's or Agent's File Reference
 (Indicated by applicant if desired) **37690-II-PCT**

Box No. I TITLE OF INVENTION
 CD4-GAMMA2 AND CD4-IgG2 CHIMERAS

Box No. II APPLICANT (WHETHER OR NOT ALSO INVENTOR); DESIGNATED STATES FOR WHICH HE / SHE / IT IS APPLICANT. Use this box for indicating the applicant or, if there are several applicants, one of them. If more than one person (includes, where applicable, a legal entity) is involved, continue in Box No. III.

The person identified in this box is (check one only): applicant and inventor* applicant only

Name and address:*

PROGENICS PHARMACEUTICALS, INC.
 Old Saw Mill River Road
 Tarrytown, New York 10591
 United States of America

Telephone number:
 (including area code)

NONE

Telegraphic address:

NONE

Telexaddress:

NONE

Country of nationality: United States of America Country of residence:*** United States of America

The person identified in this box is applicant for the purposes of (check one only):

all designated States

all designated States except
 the United States of America

the United States
 of America only

the States indicated
 in the "Supplemental Box"

Box No. III FURTHER APPLICANTS, IF ANY; (FURTHER) INVENTORS, IF ANY; DESIGNATED STATES FOR WHICH THEY ARE APPLICANTS (IF APPLICABLE). A separate sub-box has to be filled in in respect of each person (includes, where applicable, a legal entity). If the following two sub-boxes are insufficient, continue in the "Supplemental Box," (giving there for each additional person the same indications as those requested in the following two sub-boxes) or by using a "continuation sheet."

The person identified in this sub-box is (check one only): applicant and inventor* applicant only inventor only

Name and address:*

BEAUDRY, GARY A.
 109 Inwood Avenue
 Upper Montclair, New Jersey 07043
 United States of America

If the person identified in this sub-box is applicant (or applicant and inventor), indicate also:

Country of nationality: United States of America Country of residence:*** United States of America

and whether that person is applicant for the purposes of (check one only):

all designated States

all designated States except
 the United States of America

the United States
 of America only

the States indicated
 in the "Supplemental Box"

The person identified in this sub-box is (check one only): applicant and inventor* applicant only inventor only

Name and address:*

MADDON, PAUL J.
 60 Haven Avenue
 Apt. 25C
 New York, New York 10032
 United States of America

If the person identified in this sub-box is applicant (or applicant and inventor), indicate also:

Country of nationality: United States of America Country of residence:*** United States of America

and whether that person is applicant for the purposes of (check one only):

all designated States

all designated States except
 the United States of America

the United States
 of America only

the States indicated
 in the "Supplemental Box"

* If the person indicated as "applicant and inventor" or as "inventor only" is not an inventor for the purposes of all the designated States give the necessary indications in the "Supplemental box."

** Indicate the name of a natural person by giving his/her family name first followed by the given name(s). Indicate the name of a legal entity by its full official designation. In the address, include both the postal code (if any) and the country (name).

*** If residence is not indicated, it will be assumed that the country of residence is the same as the country indicated in the address.

Box No. IV AGENT (IF ANY) OR COMMON REPRESENTATIVE (IF ANY): ADDRESS FOR NOTIFICATIONS IN CERTAIN CASES. A common representative may be appointed only if there are several applicants and if no agent is or has been appointed; the common representative must be one of the applicants. The following person (includes, where applicable, a legal entity) is hereby/has been appointed as agent or common representative to act on behalf of the applicant(s) before the competent International Authorities.

Name and address, including postal code and country:

If the space below is used instead for an address for notifications, mark here

WHITE, JOHN P.
Cooper & Dunham
30 Rockefeller Plaza
New York, New York 10112
United States of America

Telephone number: 212-977-9550 Telegraphic address: KERCURTIS
(including area code)

Teleprinter address: NEW YORK 422523 COOPUT

Box No. V DESIGNATION OF GROUPS OF STATES OR STATES (1): CHOICE OF CERTAIN KINDS OF PROTECTION OR TREATMENT. The following designations are hereby made (please mark the applicable check-boxes):

Regional Patent

EP European Patent⁽²⁾: AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, DE Germany (Federal Republic of), DK Denmark, ES Spain, FR France, GB United Kingdom, IT Italy, LU Luxembourg, NL Netherlands, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT

OA OAPI Patent: Benin, Burkina Faso, Cameroon, Central African Republic, Chad, Congo, Gabon, Mali, Mauritania, Senegal, Togo, and any other State which is a Contracting State of OAPI and of the PCT. If other OAPI title desired, specify on dotted line⁽³⁾

National Patent (if other kind of protection or treatment desired, specify on dotted line⁽³⁾)

- AT Austria⁽³⁾
- AU Australia⁽³⁾
- BB Barbados
- BG Bulgaria⁽³⁾
- BR Brazil⁽³⁾
- CA Canada
- CH and LI Switzerland and Liechtenstein
- DE Germany (Federal Republic of)⁽³⁾
-
- DK Denmark
- ES Spain⁽³⁾
- FI Finland
- GB United Kingdom
- HU Hungary
- JP Japan⁽³⁾
- KP Democratic People's Republic of Korea⁽³⁾
-

- KR Republic of Korea⁽³⁾
- LK Sri Lanka
- LU Luxembourg⁽³⁾
- MC Monaco⁽³⁾
- MG Madagascar
- MW Malawi⁽³⁾
- NL Netherlands
- NO Norway
- RO Romania
- SD Sudan
- SE Sweden
- SU Soviet Union⁽³⁾
-

US United States of America⁽³⁾
CONTINUATION-IN-PART
US 08 FEBRUARY 1991 (08.02.91) 653,684

Space reserved for designating States (for the purposes of a national patent) which have become party to the PCT after the issuance of this sheet

- (1) The applicant's choice of the order of designations may be indicated by marking the check-boxes with sequential arabic numerals - see also the "Notes to Box No. V".
- (2) The selection of particular States for a European patent can be made upon entering the national (regional) phase before the European Patent Office (see also the "Notes to Box No. V").
- (3) If another kind of protection or a title of addition or, in the United States of America, treatment as a continuation or a continuation-in-part is desired, specify according to the instructions given in the "Notes to Box No. V".

Supplemental Box

If the Supplemental Box is not used, this sheet need not be included in the Request.

Use this box in the following cases:

1. If, in any of the Boxes, the space is insufficient to furnish all the information:

- (i) if more than three persons are involved as applicants and/or inventors and no "continuation sheet" is available;
- (ii) if, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked;
- (iii) if, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America;
- (iv) if there is more than one agent and their addresses are not the same;
- (v) if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," "certificate of addition," or "inventor's certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "Continuation" or "Continuation-in-part";
- (vi) if there are more than three earlier applications whose priority is claimed;

2. If the applicant claims, in respect of any designated Office, the benefits of provisions of the national law concerning non-prejudicial disclosures or exceptions to lack of novelty:

in such case, write "Continuation of Box No." [indicate the number of the Box] and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient; in particular:

in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III;

in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State or States (and/or, where applicable, European or OAPI patent) for the purposes of which the named person is applicant;

in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor and, next to such name, the State or States (and/or, where applicable, European or OAPI patent) for the purposes of which the named person is inventor;

in such case, write "Continuation of Box No. IV" and indicate for each additional agent the same type of information as required in Box No. IV;

in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of parent title or filing of parent application;

in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI.

in such case, write "Statement Concerning Non-Prejudicial Disclosures or Exceptions to Lack of Novelty" and furnish that statement below.

CONTINUATION OF BOX NO. V

US 08 FEBRUARY 1991 (08.02.91) 653,684

PCT/US92/01143

Box No. VI PRIORITY CLAIM (IF ANY). The priority of the following earlier application(s) is hereby claimed.

Country (country in which it was filed if national application; one of the countries for which it was filed if regional or international application)	Filing Date (day, month, year)	Application No.	Office of Filing (fill in only if the earlier application is an international application or a regional application)
United States of America	(08.02.91) 08 February 1991	653,684	
(2)			
(3)			

(Letter codes may be used to indicate country and/or Office of filing.)

When the earlier application was filed with the Office which, for the purposes of the present international application, is the receiving Office, the applicant may, against payment of the required fee, ask the following:

XXX the receiving Office is hereby requested to prepare and transmit to the International Bureau a certified copy of the above-mentioned earlier application(s) of the earlier applications identified above by the numbers (insert the applicable numbers) **653,684**

Box No. VII EARLIER SEARCH (IF ANY). Fill in where a search (international, international-type or other) by the International Searching Authority has already been requested (or completed) and the said Authority is now requested to base the international search, to the extent possible, on the results of the said earlier search. Identify such search or request either by reference to the relevant application (or the translation thereof) or by reference to the search request.

International application number or number and country (or regional Office) of other application:	653,684 – United States of America	International/regional/national filing date:	08 February 1991 (08.02.91)
Date of request for search:	America	Number (if available) given to search request:	

Box No. VIII SIGNATURE OF APPLICANT(S) OR AGENT
PROGENICS PHARMACEUTICALS, INC.BY: Terrence C. BurnhamDATE: 2/15/92

Name: Terrence C. Burnham

Title: President and Co-Chief Executive Officer

If the present Request form is signed on behalf of any applicant by an agent, a separate power of attorney appointing the agent and signed by the applicant is required. If in such case it is desired to make use of a general power of attorney (deposited with the receiving Office), a copy thereof must be attached to this form.

Box No. IX CHECK LIST (To be filled in by the Applicant)

This international application contains the following number of sheets:		
1. request	4	sheets
2. description	58	sheets
3. claims	5	sheets
4. abstract	1	sheets
5. drawings	27	sheets
Total	95	sheets

Figure number of the drawings (if any) is suggested to accompany the abstract for publication.

This international application as filed is accompanied by the items checked below:

1. separate signed power of attorney
2. copy of general power of attorney
3. priority document(s) (see Box No. VI)
4. receipt of the fees paid or revenue stamps (\$2,525.00)
5. cheque for the payment of fees
6. request to charge deposit account
7. other document (specify) (ASSIGNMENT)

(The following is to be filled in by the receiving Office)

1. Date of actual receipt of the purported international application
2. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application
3. Date of timely receipt of the required corrections under Article 11 of the PCT.
4. Drawings Received No Drawings

24 Rec'd PCT/PTO

10 FEB 1992

(The following is to be filled in by the International Bureau)

Date of receipt of the record copy:

Box No. VI PRIORITY CLAIM (IF ANY). The priority of the following earlier application(s) is hereby claimed.

Country (country in which it was filed if national application; one of the countries for which it was filed if regional or international application)

United States
of America

Filing Date
(day, month, year)

(08.02.91)

08 February 1991

Application No.

653,684

Office of Filing (fill in only if the earlier application is an international application or a regional application)

(2)

(3)

(Letter codes may be used to indicate country and/or Office of filing)

When the earlier application was filed with the Office which, for the purposes of the present international application, is the receiving Office, the applicant may, against payment of the required fee, ask the following:

the receiving Office is hereby requested to prepare and transmit to the International Bureau a certified copy of the above-mentioned earlier application(s)/of the earlier applications identified above by the numbers (insert the applicable numbers) 653,684

Box No. VII EARLIER SEARCH (IF ANY). Fill in where a search (international, international-type or other) by the International Searching Authority has already been requested (or completed) and the said Authority is now requested to base the international search, to the extent possible, on the results of the said earlier search. Identify such search or request either by reference to the relevant application (or the translation thereof) or by reference to the search request.

International application number or number and country (or regional Office) of other application:

653,684 - United States of America

Date of request for search:

International/regional/national filing date

08 February 1991

Number (if available)
given to search request:**Box No. VIII SIGNATURE OF APPLICANT(S) OR AGENT**

Gary A. Beaudry

Date: 2/7/92

Paul J. Maddon

Date:

If the present Request form is signed on behalf of any applicant by an agent, a separate power of attorney appointing the agent and signed by the applicant is required. If in such case it is desired to make use of a general power of attorney (deposited with the receiving Office), a copy thereof must be attached to this form.

Box No. IX CHECK LIST (To be filled in by the Applicant)

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Total	95	sheets

Figure number of the drawings (if any) is suggested to accompany the abstract for publication.

This international application as filed is accompanied by the items checked below:

1. separate signed power of attorney
2. copy of general power of attorney
3. priority document(s) (see Box No. VI)
4. receipt of the fees paid or revenue stamps
5. cheque for the payment of fees (\$2,525.00)
6. request to charge deposit account
7. other document (specify) (ASSIGNMENT)

(The following is to be filled in by the receiving Office)

1. Date of actual receipt of the purported international application:

01 Rec'd PCT/P10

10 FEB 1992

2. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application.

3. Date of timely receipt of the required corrections under Article 11 of the PCT:

4. Drawings Received No Drawings

(The following is to be filled in by the International Bureau)

Date of receipt of the record copy:

PCT/US 72/01142
RO/US 04 MAY 1992**Box No. VI PRIORITY CLAIM (IF ANY).** The priority of the following earlier applications is hereby claimed.

Country (country in which it was filed if national application; one of the countries for which it was filed if regional or international application)	Filing Date (day, month, year)	Application No.	Office of Filing (fill in only if the earlier application is an international application or a regional application)
United States of America	(08.02.91) 08 February 1991	653,684	
(2)			
(3)			

(Letter codes may be used to indicate country and/or Office of filing)

When the earlier application was filed with the Office which, for the purposes of the present international application, is the receiving Office, the applicant may, against payment of the required fee, ask the following:

 the receiving Office is hereby requested to prepare and transmit to the International Bureau a certified copy of the above-mentioned earlier application/of the earlier applications identified above by the numbers (insert the applicable numbers) 653,684**Box No. VII EARLIER SEARCH (IF ANY).** Fill in where a search (international, international-type or other) by the International Searching Authority has already been requested (or completed) and the said Authority is now requested to base the international search, to the extent possible, on the results of the said earlier search. Identify such search or request either by reference to the relevant application (or the translation thereof) or by reference to the search request.

International application number or number and country (or regional Office) of other application:

Serial No. 653,684 - United States of America

Date of request for search:

International/regional/national filing date

08 February 1991 (08.02.91)

Number (if available) given to search request:

Box No. VIII SIGNATURE OF APPLICANT(S) OR AGENT

Date:

Gary A. Beaudry

Paul J. Madden

Date:

February 19, 1992

If the present Request form is signed on behalf of any applicant by an agent, a separate power of attorney appointing the agent and signed by the applicant is required. If in such case it is desired to make use of a general power of attorney (deposited with the receiving Office), a copy thereof must be attached to this form.

Box No. IX CHECK LIST (To be filled in by the Applicant)

This international application contains the following number of sheets:	
1. request	4 sheets
2. description	58 sheets
3. claims	5 sheets
4. abstract	1 sheets
5. drawings	27 sheets
Total 95 sheets	

Figure number of the drawings (if any) is suggested to accompany the abstract for publication.

This international application as filed is accompanied by the items checked below:

- separate signed power of attorney
- copy of general power of attorney
- priority document(s) (see Box No. VI)
- receipt of the fees paid or revenue stamps
- cheque for the payment of fees (\$2,525.00)
- request to charge deposit account
- other documents (specify) (ASSIGNMENT)

(The following is to be filled in by the International Bureau)

1. Date of actual receipt of the purported international application:

01 Rec'd PCT/7PTO 10 FEB 1992

2. Corrected date of actual receipt due to later but timely received papers or drawings comprising the purported international application.

3. Date of timely receipt of the required corrections under Article 11 of the PCT:

4. Drawings Received No Drawings

(The following is to be filled in by the International Bureau)

Date of receipt of the record copy:

**PATENT COOPERATION TREATY
INTERNATIONAL SEARCH REPORT**

IDENTIFICATION OF INTERNATIONAL APPLICATION		Applicant's or Agent's File Reference 37690-II-p
International Application No. PCT/US92/01143	International Filing Date 10 FEBRUARY 1992	
Receiving Office RO/US	Priority Date Claimed 08 FEBRUARY 1991	
Applicant PROGENICS PHARMACEUTICALS, INC.		
I. <input type="checkbox"/> CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹ (Observations on supplemental sheet (2))		
II. <input checked="" type="checkbox"/> UNITY OF INVENTION IS LACKING ² (Observations on supplemental sheet (2))		
III. TITLE, ABSTRACT AND FIGURE OF DRAWING		
1. The following indicated items are approved as submitted by the applicant: ³ <input checked="" type="checkbox"/> Title. <input checked="" type="checkbox"/> Abstract.		
2. The texts established by this International Searching Authority of the following indicated items are set forth below: <input type="checkbox"/> Title. <input type="checkbox"/> Abstract.		
Text of the abstract continued on supplemental sheet		
3. a. <input type="checkbox"/> The definitive contents of the abstract are established by this International Searching Authority as proposed in form PCT/ISA/204 previously sent to the applicant. b. <input type="checkbox"/> This report is incomplete as far as the abstract is concerned as the time limit for comments by the applicant on the draft prepared by this International Search Authority has not expired ⁴ .		
4. Figure to be published with the abstract ⁵ Figure No. _____ <input checked="" type="checkbox"/> None of the figures. <input type="checkbox"/> as suggested by the applicant <input type="checkbox"/> because the applicant failed to suggest a figure <input type="checkbox"/> because this figure better characterizes the invention.		

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US92/01143

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ³		
According to International Patent Classification (IPC) or to both National Classification and IPC		
IPC (5) : C12N 15/00; A61K 39/00; C07K 13/00 US CL : 435/69.7, 70.1, 320.1; 424/85.8, 85.91; 530/387, 388		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁴		
Classification System	Classification Symbols	
U.S.	435/69.7, 70.1, 320.1; 424/85.8, 85.91; 530/387, 388	
Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched ⁵		
Please See Attached Sheet.		
III. DOCUMENTS CONSIDERED TO BE RELEVANT¹⁴		
Category*	Citation of Document, ¹⁶ with indication, where appropriate, of the relevant passages ¹⁷	Relevant to Claim No. ¹⁸
Y, P	Science, Volume 254, issued 22 November 1991, I. Pastan et al., "Recombinant Toxins for Cancer Treatment," pages 1173-1177, see entire document.	8-10, 25-27
Y	J. Biological Chemistry, Volume 264, No. 26, issued 15 September 1989, I. Pastan et al., "Pseudomonas exotoxin: chimeric toxins", pages 15157-15160. See especially page 15159, paragraphs 2-3.	8-10, 25-27
Y	Science, Volume 242, issued 25 November 1988, M.A. Till et al., "HIV-Infected cells are killed by rCD4-Ricin A Chain," pages 1166-1168, See especially Abstract.	8-10, 25-27
Y	Proc. Nat. Acad. Sci. USA, Volume 81, issued November 1984, S.L. Morrison et al., "Chimeric human antibody molecules: Mouse antigen-binding domains with human constant region domains," pages 6851-6855, see entire article.	1-4, 8-17, 25-29
Y	Nature, Volume 339, issued 04 May 1989, A. Traunecker et al, "Highly efficient neutralization of HIV with recombinant CD4-immunoglobulin molecules," pages 68-70. See entire article, especially abstract.	1-4, 8-17, 25-29
<p>* Special categories of cited documents:¹⁶</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search ² 21 APRIL 1992	Date of Mailing of this International Search Report ² 06 MAY 1992	
International Searching Authority ¹ ISA/US	Signature of Authorized Officer ²⁰ J. Marie Lorraine Spector, Ph.D. <i>J. Marie</i> <i>for</i>	

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

Y	Nature, Volume 344, issued 12 April 1990, R.A. Byrn et al., "Biological properties of a CD4 immunoadhesin," pages 667-670. See entire article, especially p.667, 1st paragraph following abstract.	1-4, 8-17, 25-29
Y	Nature, Volume 337, issued 09 February 1989, D.J. Capon et al, "Designing CD4 immunoadhesins for AIDS therapy," pages 525-531. See especially paragraph bridging pp. 525-526, last paragraph of column 1, p. 530.	1-4, 8-17, 25-29
Y	US, A, 4,664,911 (Uhr et al.) 12 May 1987, see entire document.	8-10, 25-27

V. OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE¹

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. Claim numbers __, because they relate to subject matter (1) not required to be searched by this Authority, namely:

2. Claim numbers __, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out (1), specifically:

3. Claim numbers __, because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING²

This International Searching Authority found multiple inventions in this international application as follows:

Please See Attached Sheet.

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. As all searchable claims could be searched without effort justifying an additional fee, the International Search Authority did not invite payment of any additional fee.

Remark on protest

- The additional search fees were accompanied by applicant's protest.
- No protest accompanied the payment of additional search fees.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category*	Citation of Document, ¹⁶ with indication, where appropriate, of the relevant passages ¹⁷	Relevant to Claim No. ¹⁸
Y	Cancer Research, Volume 45, issued May 1985, J.L. Murray et al, "Radioimaging in malignant melanoma with ¹¹¹ In-labeled monoclonal antibody 96.5," pages 2376-2381. See entire document.	11, 12, 28, 29
Y	WO, A, 90/01035 (Berger et al.) 08 February 1990. See especially pp. 35-38, Claims, Figure 9.	1-4, 8-17, 25-29
Y	WO, A, 89/06690 (Seed) 27 July 1989. See claims.	1-4, 8-17, 25-29
Y	WO, A, 89/02922 (Capon et al.) 06 April 1989. See Abstract, claims.	1-4, 8-17, 25-29
Y	DNA and Cell Biology, Volume 9, No. 5, issued 1990, G. Zeitmeissl et al., "Expression and characterization of human CD4: immunoglobulin fusion proteins," pages 347-353, see entire article.	1-4, 8-17, 25-29
X	Microbiol. Immunol., Volume 180, No 4., issued 1991, Chowdhury et al., "Evaluation of anti-human immunodeficiency virus effect of recombinant CD4-immunoglobulin in-vitro a good candidate for AIDS treatment," pages 183-192, see Abstract No. 92129982.	1-4, 8, 13-17, 25
Y	WO 91/00360 (Medarex) 10 January 1991, see abstract No. 91.04465.	1-4, 8-17, 25-29
Y	EP, A, 90/107393 (ROCHE) 19 April 1990, see Biosis Abstract No. 91-01425.	1-4, 8-17, 25-29

FURTHER INFORMATION CONTINUED FROM PREVIOUS SHEETS

II. FIELDS SEARCHED

Other Documents Searched:

APS (search terms: Immunotoxin, recombinant (CD4 or immunoglobulin or immunoglobulin or igg) and chimeric)
Dialog/Biochem OneSearch (search terms: chimer?(3n) (antibody or immunoglobulin or immunoglobulin or igg or cd4)

VI. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

- I. Claims 1, 3, 4, 13 and 14 drawn to a vector encoding CD4-gamma 2 chimeric heavy chain, transfection and expression thereof. Class 536 subclass 27 and class 435 subclass 320.1.
- II. Claims 2, 8-12 drawn to CD4-gamma 2 chimeric heavy chain homodimer. Class 530, subclass 388.
- III. Claims 5-7, drawn to a method of using a CD4-gamma 2 chimeric heavy chain homodimer to treat HIV. Class 424, subclasses 85.8 and 85.91.
- IV. Claim 14, drawn to a vector encoding the light chains of a CD4-IgG2 chimeric heterotetramer. Class 536, subclass 27 and class 435, subclass 320.1.
- V. Claims 15-17 and 25-19, drawn to CD4-IgG2 chimeric heterotetramers. Class 530, subclass 387.
- VI. Claims 18-21, drawn to production of CD4-IgG2 chimeric heterotetramers via expression of the vectors of groups I and IV. Class 435, subclasses 69.7 and 70.1.
- VII. Claims 22-24, drawn to a method of using CD4-IgG2 chimeric heterotetramers to treat HIV. Class 424, subclasses 85.8 and 85.91.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Gary Beaudry and Paul J. Maddon
Serial No. : 08/485,163 Examiner: K. Brown
Filed : June 7, 1995 Group Art Unit: 1812
For : CD4 GAMMA2 AND CD4-IgG2 CHIMERAS

1185 Avenue of the Americas
New York, New York 10036
May 13, 1997

Assistant Commissioner for Patents
Washington, D.C. 20231

SIR:

**STATEMENT OF COMPLIANCE
UNDER 37 C.F.R. §1.821(f)
IN CONNECTION WITH ABOVE-IDENTIFIED APPLICATION**

Pursuant to 37 C.F.R. §1.821(f), I hereby certify that the content of the Sequence Listing enclosed as Exhibit A, the papers and the content of the computer readable form of the sequence listing are identical.

Respectfully submitted,

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Applicants : Gary Beaudry and
Paul J. Maddon
Serial No. : 08/485,163
Filed : June 7, 1995
Exhibit B

reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Kaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See MPEP § 2143 – § 2143.03 for decisions pertinent to each of these criteria.

The initial burden is on the examiner to provide some suggestion of the desirability of doing what the inventor has done. "To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). See MPEP § 2144 – § 2144.09 for examples of reasoning supporting obviousness rejections.

When the motivation to combine the teachings of the references is not immediately apparent, it is the duty of the examiner to explain why the combination of the teachings is proper. *Ex parte Skinner*, 2 USPQ2d 1788 (Bd. Pat. App. & Inter. 1986). A statement of a rejection that includes a large number of rejections must explain with reasonable specificity at least one rejection, otherwise the examiner procedurally fails to establish a *prima facie* case of obviousness. *Ex parte Blanc*, 13 USPQ2d 1383 (Bd. Pat. App. & Inter. 1989) (Rejection based on nine references which included at least 40 prior art rejections without explaining any one rejection with reasonable specificity was reversed as procedurally failing to establish a *prima facie* case of obviousness.).

If the examiner determines there is factual support for rejecting the claimed invention under 35 U.S.C. 103, the examiner must then consider any evidence supporting the patentability of the claimed invention, such as any evidence in the specification or any other evidence submitted by the applicant. The ultimate determination of patentability is based on the entire record, by a preponderance of evidence, with due consideration to the persuasiveness of any arguments and any secondary evidence. *In re Getiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). The legal standard of "a preponderance of evidence" requires the evidence to be more convincing than the evidence which is offered in opposition to it.

With regard to rejections under 35 U.S.C. 103, the examiner must provide evidence which as a whole shows that the legal determination sought to be proved (i.e., the reference teachings establish a *prima facie* case of obviousness) is more probable than not.

When an applicant submits evidence, whether in the specification as originally filed or in response to a rejection, the examiner must reconsider the patentability of the claimed invention. The decision on patentability must be made based upon consideration of all the evidence, including the evidence submitted by the examiner and the evidence submitted by the applicant. A decision to make or maintain a rejection in the face of all the evidence must show that it was based on the totality of the evidence. Facts established by rebuttal evidence must be evaluated along with the facts on which the conclusion of obviousness was reached, not against the conclusion itself. *In re Eli Lilly & Co.*, 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990).

See *In re Piasecki*, 745 F.2d 1468, 223 USPQ 785 (Fed. Cir. 1984) for a discussion of the proper roles of the examiner's *prima facie* case and applicant's rebuttal evidence in the final determination of obviousness. See MPEP § 706.02(j) for a discussion of the proper contents of a rejection under 35 U.S.C. 103. <

2143 Basic Requirements of a *Prima Facie* Case of Obviousness [R-1]

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Kaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). <

means can be run at a variable speed, however the court found that this does not require that the output pump be run at the claimed speed so that air is drawn into the mixing chamber and is entrained in the ingredients during operation. Although a prior art device "may be capable of being modified to run the way the apparatus is claimed, there must be a suggestion or motivation in the reference to do so." 16 USPQ2d at 1432.). See also *In re Fritch*, 972 F.2d 1260, 23 USPQ2d 1780 (Fed. Cir. 1992) (flexible landscape edging device which is conformable to a ground surface of varying slope not suggested by combination of prior art references).

FACT THAT THE CLAIMED INVENTION IS WITHIN THE CAPABILITIES OF ONE OF ORDINARY SKILL IN THE ART IS NOT SUFFICIENT BY ITSELF TO ESTABLISH PRIMA FACIE OBVIOUSNESS

A statement that modifications of the prior art to meet the claimed invention would have been "well within the ordinary skill of the art at the time the claimed invention was made" because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levingood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993).

THE PROPOSED MODIFICATION CANNOT RENDER THE PRIOR ART UNSATISFACTORY FOR ITS INTENDED PURPOSE

If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984) (Claimed device was a blood filter assembly for use during medical procedures wherein both the inlet and outlet for the blood were located at the bottom end of the filter assembly, and wherein a gas vent was present at the top of the filter assembly. The prior art reference taught a liquid strainer for removing dirt and water from gasoline and other light oils wherein the inlet and outlet were at the top of the device, and wherein a pet-cock (stopcock) was located at the bottom of the device for periodically removing the

collected dirt and water. The reference further taught that the separation is assisted by gravity. The Board concluded the claims were *prima facie* obvious, reasoning that it would have been obvious to turn the reference device upside down. The court reversed, finding that if the prior art device was turned upside down it would be inoperable for its intended purpose because the gasoline to be filtered would be trapped at the top, the water and heavier oils sought to be separated would flow out of the outlet instead of the purified gasoline, and the screen would become clogged.).

THE PROPOSED MODIFICATION CANNOT CHANGE THE PRINCIPLE OF OPERATION OF A REFERENCE

If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959) (Claims were directed to an oil seal comprising a bore engaging portion with outwardly biased resilient spring fingers inserted in a resilient sealing member. The primary reference relied upon in a rejection based on a combination of references disclosed an oil seal wherein the bore engaging portion was reinforced by a cylindrical sheet metal casing. Patentee taught the device required rigidity for operation, whereas the claimed invention required resiliency. The court reversed the rejection holding the "suggested combination of references would require a substantial reconstruction and redesign of the elements shown in [the primary reference] as well as a change in the basic principle under which the [primary reference] construction was designed to operate." 123 USPQ at 352.).<

2143.02 Reasonable Expectation of Success Is Required [R-1]

>OBVIOUSNESS REQUIRES ONLY A REASONABLE EXPECTATION OF SUCCESS

The prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success. *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986) (Claims directed to a method of treating depression with

**2144.09 Close Structural Similarity
Between Chemical Compounds
(Homologs, Analogues, Isomers)
[R-1]**

> REJECTION BASED ON CLOSE STRUCTURAL SIMILARITY IS FOUNDED ON THE EXPECTATION THAT COMPOUNDS SIMILAR IN STRUCTURE WILL HAVE SIMILAR PROPERTIES

A *prima facie* case of obviousness may be made when chemical compounds have very close structural similarities and similar utilities. "An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties." *In re Payne*, 606 F.2d 303, 203 USPQ 245, 254 (CCPA 1979). See *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) (discussed in more detail below) and *In re Dillon*, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1991) (discussed below and in MPEP § 2144) for an extensive review of the case law pertaining to obviousness based on close structural similarity of chemical compounds.

HOMOLOGY AND ISOMERISM ARE FACTS WHICH MUST BE CONSIDERED WITH ALL OTHER RELEVANT FACTS IN DETERMINING OBVIOUSNESS

Compounds which are position isomers (compounds having the same radicals in physically different positions on the same nucleus) or homologs (compounds differing regularly by the successive addition of the same chemical group, e.g., by $-\text{CH}_2-$ groups) are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. *In re Wilder*, 563 F.2d 457, 195 USPQ 426 (CCPA 1977). See also *In re May*, 574 F.2d 1082, 197 USPQ 601 (CCPA 1978) (stereoisomers *prima facie* obvious).

Isomers having the same empirical formula but different structures are not necessarily considered equivalent by chemists skilled in the art and therefore are not necessarily suggestive of each other. *Ex parte Mowry*, 91 USPQ 219 (Bd. App. 1950) (claimed cyclohexylstyrene not *prima facie* obvious over prior art isohexylstyrene).

rene). Similarly, homologs which are far removed from adjacent homologs may not be expected to have similar properties. *In re Mills*, 281 F.2d 218, 126 USPQ 513 (CCPA 1960) (prior art disclosure of C₈ to C₁₂ alkyl sulfates was not sufficient to render *prima facie* obvious claimed C₁ alkyl sulfate).

Homology and isomerism involve close structural similarity which must be considered with all other relevant facts in determining the issue of obviousness. *In re Mills*, 281 F.2d 218, 126 USPQ 513 (CCPA 1960); *In re Wiechers*, 370 F.2d 927, 152 USPQ 247 (CCPA 1967); Homology should not be automatically equated with *prima facie* obviousness because the claimed invention and the prior art must each be viewed "as a whole." *In re Langer*, 465 F.2d 896, 175 USPQ 169 (CCPA 1972) (Claims to a polymerization process using a sterically hindered amine were held unobvious over a similar prior art process because the prior art disclosed a large number of unhindered amines and only one sterically hindered amine (which differed from a claimed amine by 3 carbon atoms), and therefore the reference as a whole did not apprise the ordinary artisan of the significance of hindered amines as a class.).

PRESENCE OF A TRUE HOMOLOGOUS OR ISOMERIC RELATIONSHIP IS NOT CONTROLLING

Prior art structures do not have to be true homologs or isomers to render structurally similar compounds *prima facie* obvious. *In re Payne*, 606 F.2d 303, 203 USPQ 245 (CCPA 1979) (Claimed and prior art compounds were both directed to heterocyclic carbamoyloximino compounds having pesticidal activity. The only structural difference between the claimed and prior art compounds was that the ring structures of the claimed compounds had two carbon atoms between two sulfur atoms whereas the prior art ring structures had either one or three carbon atoms between two sulfur atoms. The court held that although the prior art compounds were not true homologs or isomers of the claimed compounds, the similarity between the chemical structures and properties is sufficiently close that one of ordinary skill in the art would have been motivated to make the claimed compounds in searching for new pesticides.).

See also *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986) (claimed and prior art compounds used in a method of treating depression

2144.09

would have been expected to have similar activity because the structural difference between the compounds involved a known bioisosteric replacement) (see MPEP § 2144.08 for a more detailed discussion of the facts in the *Merck* case); *In re Dillon*, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1991) (The tri-orthoester fuel compositions of the prior art and the claimed tetra-orthoester fuel compositions would have been expected to have similar properties based on close structural and chemical similarity between the orthoesters and the fact that both the prior art and applicant used the orthoesters as fuel additives) (see MPEP § 2144 for a more detailed discussion of the facts in the *Dillon* case.).

Compare *In re Grabiak*, 769 F.2d 729, 226 USPQ 871 (Fed. Cir. 1985) (substitution of a thioester group for an ester group in an herbicidal safener compound was not suggested by the prior art); *In re Bell*, 991 F.2d 781, 26 USPQ2d 1529 (Fed. Cir. 1993) (The established relationship between a nucleic acid and the protein it encodes in the genetic code does not render a gene *prima facie* obvious over its corresponding protein in the same way that closely related structures in chemistry may create a *prima facie* case because there are a vast number of nucleotide sequences that might encode for a specific protein as a result of degeneracy in the genetic code (i.e., the fact that most amino acids are specified by more than one nucleotide sequence or codon).); *In re Deuel*, 94-1202 (Fed. Cir. 1995) ("A prior art disclosure of the amino acid sequence of a protein does not necessarily render particular DNA molecules encoding the protein obvious because the redundancy of the genetic code permits one to hypothesize an enormous number of DNA sequences coding for the protein." The existence of a general method of gene cloning in the prior art is not sufficient, without more, to render obvious a particular cDNA molecule.).

CLAIMED COMPOUNDS ARE UNOBIUS WHERE PRIOR ART DOES NOT TEACH OR SUGGEST A METHOD FOR MAKING THE CLAIMED COMPOUND

"[I]f the prior art of record fails to disclose or render obvious a method for making a claimed compound, at the time the invention was made, it may not be legally concluded that the compound itself is in the possession of the public. In this context, we say that the absence of a known or obvious process for making the claimed com-

pounds overcomes the presumption that the compounds are obvious, based on the close relationships between their structures and those of prior art compounds." *In re Hoeksema*, 399 F.2d 269, 158 USPQ 597, 601 (CCPA 1968). See also *In re Payne*, 606 F.2d 303, 203 USPQ 245 (CCPA 1979) for a general discussion of circumstances under which the prior art suggests methods for making novel compounds which are of close structural similarity to compounds known in the prior art.

PRESUMPTION OF OBVIOUSNESS BASED ON STRUCTURAL SIMILARITY IS OVERCOME WHERE THERE IS NO REASONABLE EXPECTATION OF SIMILAR PROPERTIES

The presumption of obviousness based on a reference disclosing structurally similar compounds may be overcome where there is evidence showing there is no reasonable expectation of similar properties in structurally similar compounds. *In re May*, 574 F.2d 1082, 197 USPQ 601 (CCPA 1978) (appellant produced sufficient evidence to establish a substantial degree of unpredictability in the pertinent art area, and thereby rebutted the presumption that structurally similar compounds have similar properties); *In re Schechter*, 205 F.2d 185, 98 USPQ 144 (CCPA 1953). See also *Ex parte Blattner*, 2 USPQ2d 2047 (Bd. Pat. App. & Inter. 1987) (Claims directed to compounds containing a 7-membered ring were rejected as *prima facie* obvious over a reference which taught 5- and 6-membered ring homologs of the claimed compounds. The Board reversed the rejection because the prior art taught that the compounds containing a 5-membered ring possessed the opposite utility of the compounds containing the 6-membered ring, undermining the examiner's asserted *prima facie* case arising from an expectation of similar results in the claimed compounds which contain a 7-membered ring.).

IF PRIOR ART COMPOUNDS HAVE NO UTILITY, OR UTILITY ONLY AS INTERMEDIATES, CLAIMED STRUCTURALLY SIMILAR COMPOUNDS MAY NOT BE PRIMA FACIE OBVIOUS OVER THE PRIOR ART

If the prior art does not teach any specific or significant utility for the disclosed compounds, then the prior art is not sufficient to render structurally similar claims

prima facie obvious because there is no motivation for one of ordinary skill in the art to make the reference compounds, much less any structurally related compounds. *In re Stemniski*, 444 F.2d 581, 170 USPQ 343 (CCPA 1971).

Where structurally similar "prior art compounds 'cannot be regarded as useful' for the sole use disclosed [by the reference], . . . a person having ordinary skill in the art would lack the 'necessary impetus' to make the claimed compounds." *In re Albrecht*, 514 F.2d 1389, 185 USPQ 585, 590 (CCPA 1975) (prior art reference studied the local anesthetic activity of various compounds, and taught that compounds structurally similar to those claimed were irritating to human skin and therefore "cannot be regarded as useful anesthetics.") 185 USPQ at 587.)

Similarly, if the prior art merely discloses compounds as intermediates in the production of a final product, one of ordinary skill in the art would not have been motivated to stop the reference synthesis and investigate the intermediate compounds with an expectation of arriving at claimed compounds which have different uses. *In re Lalu*, 747 F.2d 703, 223 USPQ 1257 (Fed. Cir. 1984).

PRIMA FACIE CASE REBUTTABLE BY EVIDENCE OF SUPERIOR OR UNEXPECTED RESULTS

A *prima facie* case of obviousness based on structural similarity is rebuttable by proof that the claimed compounds possess unexpectedly advantageous or superior properties. *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) (Affidavit evidence which showed that claimed triethylated compounds possessed anti-inflammatory activity whereas prior art trimethylated compounds did not was sufficient to overcome obviousness rejection based on the homologous relationship between the prior art and claimed compounds.); *In re Wiechart*, 370 F.2d 927, 152 USPQ 247 (CCPA 1967) (a 7-fold improvement of activity over the prior art held sufficient to rebut *prima facie* obviousness based on close structural similarity).

However, a claimed compound may be obvious because it was suggested by, or structurally similar to, a prior art compound even though a particular benefit of the claimed compound asserted by patentee is not expressly disclosed in the prior art. It is the differences in fact in their respective properties which are determina-

tive of nonobviousness. If the prior art compound does in fact possess a particular benefit, even though the benefit is not recognized in the prior art, applicant's recognition of the benefit is not in itself sufficient to distinguish the claimed compound from the prior art. *In re Dillon*, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1991).

See MPEP § 716.02 – § 716.02(g) for a discussion of evidence alleging unexpectedly advantageous or superior results.<

2145 Consideration of Applicant's Rebuttal Arguments [R-2]

(a) Argument does not replace evidence where evidence is necessary

Attorney argument is not evidence unless it is an admission, in which case, an Examiner may use the admission in making a rejection. See MPEP § 2129 and § 2144.03 for a discussion of admissions as prior art.

The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). See MPEP § 716.01(c) for examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration.

(b) Arguing additional advantages or latent properties

PRIMA FACIE OBVIOUSNESS IS NOT REBUTTED BY MERELY RECOGNIZING ADDITIONAL ADVANTAGES OR LATENT PROPERTIES PRESENT IN THE PRIOR ART

Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. *In re Wiseman*, 596 F.2d 1019, 201 USPQ 658 (CCPA 1979) (Claims were directed to grooved carbon disc brakes wherein the grooves were provided to vent steam or vapor during a braking action. A prior art reference taught noncarbon disc brakes which were grooved for the purpose of cooling the faces of the braking members and eliminating dust. The court held the prior art references when combined would overcome the problems of dust and overheating solved by the prior art and would inherently overcome the steam or vapor cause of the problem relied upon for patentability by applicants. Granting a patent on the discovery of an unknown but inherent function (here venting steam or vapor) "would re-



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